REMARKS/ARGUMENTS

The foregoing amendments in the specification and claims are of a formal nature, and do not add new matter.

Applicants note and appreciate the withdrawal of the earlier objections and rejections under 35 U.S.C. §112, first paragraph, and second paragraph and rejections under 35 U.S.C. §102(b).

Prior to the present amendment, Claims 33-35, 38-40 and 44-43 were pending in this application and were rejected on various grounds. With this amendment, Claims 34-35 have been canceled without prejudice and Claims 46 and 48 have been amended to clarify what applicants have always regarded as their invention.

Claims 33, 38-40 and 44-54 are pending after entry of the instant amendment.

Applicants note that although page 1 of the instant Office Action indicates that Claims 48-54 are rejection, the Examiner did not indicate reasons for rejecting these claims in the instant Office Action. Accordingly, Applicants assume that Claims 48-54 are allowable and an indication of such is respectfully requested.

Applicants expressly reserve the right to pursue any canceled matter in subsequent continuation, divisional or continuation-in-part applications.

Priority Determination

The Examiner stated that the effective filing date for the application is December 13, 2001, the filing date of the instant application. The Examiner alleges that "the Provisional patent applications listed, although disclosing the same experimental assays as the instant specification, do not enable the instant invention and therefore do not impart Utility to the claims of the current application."

Applicants respectfully disagree.

Applicants rely on the gene amplification assay (Example 143) for patentable utility which was first disclosed in U.S. Provisional Patent Application Serial No. 60/162,506, filed October 29, 1999, priority to which has been claimed in this application. Further, the Examiner has admitted that the U.S. Provisional Patent Application Serial No. 60/162,506 discloses the

same gene amplification assay as the instant application. Therefore, Applicants respectfully submit that all claim limitations are fully supported by the disclosure of U.S. Provisional Patent Application Serial No. 60/162,506, filed on October 29, 1999.

Claim Rejections – 35 U.S.C. §101 and §112, First Paragraph

Claims 33-35, 38-40 and 44-47 remain rejected under 35 U.S.C. §101, allegedly "because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility." The Claims 33-35, 38-40 and 44-47 further remain rejected under 35 U.S.C. §112, first paragraph, allegedly "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility ... one skilled in the art clearly would not know how to use the claimed invention."

The Examiner notes that Applicants argue (16 September 2004, page 8) that "the PRO1555 nucleic acid is a diagnostic marker for variety of normal and cancerous tissues, and point to the results of the amplification assay (page 11, 16 September 2004)." However, Examiner states that "Applicant's arguments (16 September 2004) have been fully considered but are not found to be persuasive."

The Examiner alleges that "the specification provides data showing a very small increase in DNA copy number-about 2.3 fold- in many types of normal and cancerous types of tumor. However there is no evidence regarding whether or not PRO1555 mRNA or polypeptide levels are also increased in these cancers." (See page 5 of the instant Office Action, emphasis added). Therefore, the Examiner concludes, "the Specification's assertions that the claimed PRO1555 polypeptides have utility in the fields of cancer diagnostics and cancer therapeutics are not substantial." (See page 6 of the instant Office Action).

Thus, it appears to the Applicants that the Examiner's rejections for lack of utility in the instant Office Action are mostly directed to the alleged lack of utility for the PRO1555 polypeptide. (See pages 4-8 of the instant Office Action). In response, Applicants respectfully submit that present application is directed to the PRO1555 nucleic acids and not the PRO1555 polypeptides.

The Examiner also alleges:

> The PRO1555 gene has *not* been associated with tumor formation or the development of cancer, nor has it been shown to be predictive of such. The specification merely demonstrates that the PRO1555 nucleic acid was amplified in some cancers, to a minor degree, of 2.5 fold increase. No mutation or translocation of PRO1555 has been associated with any type of cancer versus normal tissue. It is not known whether PRO1555 is expressed in corresponding normal lung or colon tissue, and what the relative levels of expression are. In the absence of any of the above information, all that the specification does is present evidence that the DNA encoding PRO1555 is amplified in a variety of samples, including some normal tissues, and invites the artisan to determine the significance of this increase.

See page 7 of the instant Office Action.

Applicants strongly disagree and traverse the rejection. Further, Applicants submit that the cancellation of Claims 34 and 35 renders the rejection of these claims moot.

Applicants respectfully maintain the position that that the specification discloses at least one credible, substantial and specific asserted utility for the PRO1555 nucleic acids for the reasons previously set forth in the Applicants' response filed on September 16, 2004.

Furthermore, as discussed in the Applicants' response of September 16, 2004, the nucleic acids encoding PRO1555 had ΔCt value of > 1.0 for (1) in primary lung tumors: LT13, LT15, LT16, HF-000631, HF-000840, and HF-000842; (2) in lung cell lines: A549, Calu-1, Calu-6, H441, H460, and SKMES1; (3) in primary colon tumors: CT15, CT16, CT17, and colon tumor centers HF-000539 and HF-000575; (4) in colon cell lines: SW620, Colo320 and HCT116; (5) in breast tumor center HF-000545; (6) in kidney tumor center HF-000611; and (7) in testis tumor margin HF-000716 and testis tumor center HF-000733. PRO1555 showed approximately 1.04-4.99 ΔCt units which corresponds to $2^{1.04}$-$2^{4.99}$ fold amplification or **2.056 fold to 31.779**-fold amplification in these tumors.

Therefore, contrary to the Examiner's assertion on page 4 of the Office Action that the specification provides data showing a very small increase in DNA copy number, Applicants submit that the PRO1555 nucleic acid was amplified in a significant number of lung, colon, breast, kidney and testis tumors and showed 2.056 to 31,779 fold amplification in these tumors.

In addition, the previously submitted Declaration by Dr. Audrey Goddard clearly states:

> It is further my considered scientific opinion that an at least **2-fold increase** in gene copy number in a tumor tissue sample relative to a normal (*i.e.*, non-tumor) sample is significant and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number as quantitated by the TaqMan PCR technique as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. Accordingly, a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is **useful as a marker for the diagnosis of cancer**, for monitoring cancer development and/or for measuring the efficacy of cancer therapy. (Emphasis added).

Therefore, any gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay is considered useful as a marker for the diagnosis of cancer.

Finally, the Examiner alleges, "[o]ne cannot determine from the data in the specification whether the observed 'amplification' of nucleic acid is due to increase in chromosomal copy number, or alternatively due to an increase in transcription rates." (See pages 7 of the instant Office Action).

In response, Applicants refer to the previously submitted Declaration by Dr. Avi Ashkenazi, Ph.D. In particular, Dr. Ashkenazi is in opinion that gene amplification of a gene, whether by aneuploidy or any other mechanism, is still useful as a diagnostic marker. As a result, the present gene amplification assay is a well-controlled experiment and give rise to data of biological significance. As Dr. Ashkenazi explains,

> An increase in gene copy number can result not only from intrachromosomal changes but also from chromosomal aneuploidy. It is important to understand that detection of gene amplification can be used for cancer diagnosis even if the determination includes measurement of chromosomal aneuploidy. Indeed, as long as a significant difference relative to normal tissue is detected, it is irrelevant if the signal originates from an increase in the number of gene copies per chromosome and/or an abnormal number of chromosomes.

Accordingly, Applicants respectfully submit that Applicants have shown that the present application discloses at least one patentable utility for the PRO1555 nucleic acids.

Furthermore, based on the instant disclosure and the advanced knowledge in the art at the time of filing, one skilled in the art would know exactly how to make and use these nucleic acids

for the diagnosis of variety of tumors; for example, by using diagnostic methods based on hybridization to such amplified sequences.

In view of the above, Applicants respectfully request the Examiner to reconsider and withdraw the rejection of under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph.

CONCLUSION

All claims pending in the present application are believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641**, referencing Attorney's Docket No. **39780-2830 P1C63**). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: February 28, 2005

By: _____
Anna L. Barry (Reg. No. 51,436)

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